

## REMARKS

Claims 2-92, 105, 106, 108, and 109 were previously canceled. Claims 1, 110, 112, 115 and 121 have been amended to more particularly point out and distinctly claim that which the Applicants regard as the invention. Claims 97, 99 and 113 have been amended for consistency in use of the term “ $\beta$ -APP.” The amendments to the claims are fully supported by the specification as filed. Accordingly, no new matter is added. Upon entry of this amendment claims 1, 93-104, 107 and 110-121 will be pending and under examination. Consideration of the present application is respectfully requested in view of the following remarks.

### **Claim Rejections - 35 U.S.C. § 112, second paragraph**

In the Non-Final Office Action mailed April 29, 2008, the Examiner rejected claims 1 and 110-120 under 35 U.S.C. § 112, second paragraph for lacking proper antecedent basis. Claims 1, 110, 112, and 115 have been amended to replace the term “neuronal cells” with the term “cells expressing CD40R and  $\beta$ -APP” in order to provide proper antecedent basis. Applicants submit the amendments to the claims obviate the rejection and respectfully request that the rejection be withdrawn.

### **Claim Rejections - 35 U.S.C. § 112, first paragraph**

In the Non-Final Office Action mailed April 29, 2008, the Examiner rejected claims 1, 93, 94, 96, 97, 99, 107 and 112-121 under 35 U.S.C. § 112, first paragraph as introducing new matter. Specifically, the Examiner alleges the amendment to delete reference to neuronal cells and include the term “cells that express CD40R and  $\beta$ -APP” is considered new matter. Applicants respectfully traverse the rejection.

An *in vitro* method for screening compounds that modulate the CD40L/CD40R signaling pathway is described in [0093]. The method comprises contacting a cell that expresses CD40R and  $\beta$ -amyloid precursor protein ( $\beta$ -APP) with a compound (CD40 ligand) and measuring the level of  $\beta$ -APP or a fragment thereof. The method requires that the cell express both CD40R and  $\beta$ -APP. However, the specification does not

specify that methods of the present invention require cells that naturally express either CD40R or  $\beta$ -APP. The specification states at [0034] that “[v]arious other cells, in addition to CNS cells and peripheral cells, can be used to determine the modulatory effect of test compounds according to the methods of the present invention. The specification goes on to state that “[e]xamples of other such cells include, without limitation, cell lines derived from CNS cells, cell lines derived from peripheral cells, transgenic cells, transgenic cells derived from transgenic animals, or human cells or cell lines.” Therefore, one of ordinary skill in the art would recognize that the methods of the present invention encompass the use of any cell expressing both CD40R and/or  $\beta$ -APP, including cells naturally expressing CD40R and  $\beta$ -APP as well as transgenic cells modified to express one or both of CD40R and  $\beta$ -APP. The fact that the working example of [0093] uses a neuronal cell that naturally expresses CD40R does not negate the disclosure of [0034], which clearly states that non-CNS, transgenic cell lines, may be used in the methods of the present invention. Therefore, the specification does provide adequate support under 35 U.S.C. § 112, first paragraph for the limitation “cells that express CD40R and  $\beta$ -APP”, and no new matter has been added. Accordingly, Applicants respectfully request the rejection under 35 U.S.C. § 112, first paragraph be withdrawn.

#### **Claim Rejections - 35 U.S.C. § 103(a)**

In the Non-Final Office Action mailed April 29, 2008, the Examiner rejected claims 1, 93, 94, 96, 97, 99, 100, 107, and 110-112 under 35 U.S.C. § 103(a) as unpatentable over Tan et al. (Science, 1999, 286:2352-2355, hereinafter “Tan”) in view of Gehrmann et al. (Glia, 1995, 15:141-151, hereinafter “Gehrmann”), Gerritse et al. (PNAS, 1996, 93:2499-2504, hereinafter “Gerritse”), LeBlanc et al. (J. Neurochem., 1996, 66:2300-2310, hereinafter “LeBlanc”) and Tan et al. (EMBO J., 2002, 21:643-652). Applicants respectfully traverse the rejection.

In relevant part, the Examiner alleges that Tan teaches a method for testing the ability of monoclonal antibodies directed against CD40R to interfere with the CD40L/CD40R signaling pathway in microglia using TNF- $\alpha$  expression as a marker for modulation of both the signaling pathway and microglial activation. The Examiner then

alleges that the prior art demonstrates 1) that CD40L binding molecules modulate the CD40L/CD40R signaling pathway (Gerritse); and 2) that  $\beta$ -APP expression is increased in activated microglia (Gehrmann). In view of these teachings, the Examiner contends that one of skill in the art would be motivated to substitute the expression of TNF- $\alpha$  taught by Tan with the expression of  $\beta$ -APP as taught by Gehrmann. The Examiner further alleges that the prior art demonstrates that microglia process  $\beta$ -APP to yield A $\beta$  as evidenced by LeBlanc, which presumably leads to the suggestion that the expression of A $\beta$  could be substituted for that of  $\beta$ -APP as in Gehrmann and, thus, for that of TNF- $\alpha$  as in Tan.

Gehrmann is a study of the expression of  $\beta$ -APP and its proteolytic fragments in varying neuronal cells during the development of brain lesions associated with Multiple Sclerosis (MS). However, Gehrmann neither teaches nor suggests that the expression of  $\beta$ -APP in microglial cells is dependent on the activation state of the cells. Although Gehrmann reports that activated microglia in actively demyelinating lesions of MS express  $\beta$ -APP, the reference also indicates that  $\beta$ -APP expression was found on microglia within control tissues: teaching that non-activated microglia also express  $\beta$ -APP (see Gehrmann, page 145, first column, lines 2-7 and FIG.1). Thus, contrary to the assertions of the Examiner, the teachings of Gehrmann demonstrate that  $\beta$ -APP expression may be indicative of active MS lesions, but not that  $\beta$ -APP is a marker of microglial activation. In fact, one of skill in the art would interpret the teachings of Gehrmann to demonstrate that  $\beta$ -APP expression is not linked to the activation state of a microglial cell. Accordingly, Gehrmann provides no suggestion that the expression of  $\beta$ -APP could be substituted for that of TNF- $\alpha$  as a marker for microglial activation or the modulation of CD40L/CD40R signaling as taught by Tan.

In addition, with respect to a contention for the further replacement of the expression of  $\beta$ -APP as a marker for microglial activation and/or modulation of CD40L/CD40R signaling, nowhere does the art demonstrate that the expression of A $\beta$  may substitute for that of  $\beta$ -APP as such a marker. The Examiner references LeBlanc as an alleged teaching that microglia process  $\beta$ -APP to yield A $\beta$  (citing LeBlanc, page 2303, column 2). However, the reference in fact teaches the exact opposite of the Examiner's

contention. Although the passage cited by the Examiner indicates that microglia express the full length  $\beta$ -APP protein, it is completely silent as to the protein's further processing in these cells. Where the processing of  $\beta$ -APP to yield A $\beta$  is discussed (LeBlanc, page 2304 column 2, line 13 to page 2305, column 1, line 6), LeBlanc reports that microglia process  $\beta$ -APP to form only p3 (a non-amyloidogenic fragment of  $\beta$ -APP) and not A $\beta$  (see, in particular, LeBlanc, page 2305, column 1, lines 3-6 and FIGS. 4 B and C). Thus, in view of LeBlanc, one of skill in the art would not view the expression of A $\beta$  as a substitute for the expression of  $\beta$ -APP in any assay, generally, much less as a marker of microglial activation and/or the modulation of the CD40L/CD40R signaling pathway.

Moreover, nowhere in any reference cited by the Examiner is shown that modulation of CD40 activity led to a modulation in APP expression/processing. Only in the present application is it shown that direct modulation of CD40R activity correlates with a modulation of APP processing [0093]. Gerriste is directed to an evaluation of activated microglia in the etiology of MS in a model system, but is completely silent with respect to  $\beta$ -APP expression, thus cannot render the instant claims obvious.

Absent the link established in the instant application between CD40 activity and  $\beta$ -APP expression, it is impossible for one of ordinary skill in the art to conclude that  $\beta$ -APP is associated with microglial activation, much less that CD40 activity and  $\beta$ -APP expression are interdependent events as instantly claimed. The conclusion that  $\beta$ -APP expression in microglia cells is directly correlated to modulation of the CD40L/CD40R signaling pathway is beyond the inferences and creative steps a person of ordinary skill in the art could make without direct experimental evidence as provided in the instant application. Therefore, one of ordinary skill in the art would not have a reasonable expectation of success in using  $\beta$ -APP as a marker of CD40L/CD40R signal pathway modulation based on the teaching of Gehrman and Gerritse, and would not be motivated to replace TNF- $\alpha$  with  $\beta$ -amyloid in the method of Tan.

For at least the foregoing, Applicants submit the rejection under 35 U.S.C. § 103(a) has been overcome and respectfully request that it be withdrawn.

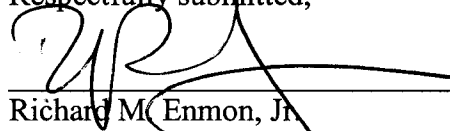
### **CONCLUSION**

Applicant respectfully requests that the amendment and remarks made herein be entered and made of record in the instant application. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

No fees are believed to be due in connection with this response other than that authorized in the petition for extension of time submitted concurrently herewith. However, in the event that additional fees are required, the Commissioner is hereby authorized to charge any underpayment or credit any overpayment of fees to Deposit Account No. 50-3732, order number 12062-1085020.

Date: October 29, 2008

Respectfully submitted,



Richard M. Enmon, Jr.

**KING & SPALDING**

1185 Avenue of the Americas  
New York, New York 10036  
(212) 556-2100

52,865

(Reg. No.)